

Remarks

Claims 1-15 and 22-24 are pending in the present application. Claims 16-21, directed to compositions, were previously cancelled in an effort to expedite the allowance of the instant application. Claims 23-24 were previously added to the present application. Applicants consider the claims allowable in their presently amended form. Consequently, no amendment has been made to the previously submitted claims. The response is filed here to present the declaration of Dr. John Vanden Heuvel, a co-inventor of the subject matter of the present invention, in support of the patentability of the present invention. This response is also filed to expedite allowance of instant application or to narrow the issues which may be determined on appeal.

In the September 22, 2004 office action, the Examiner withdrew the previously presented rejections and newly rejected the previously filed claims based upon his view that those claims are obvious under 35 U.S.C. §103 over the combined teachings of de Boer, et al., U.S. patent number 5,518,751 ("de Boer"), in view of Cook, et al., U.S. patent number 5,554,646 ("Cook") and the article *Diabetes Mellitus* in Pharmacotherapy: A Pathophysiologic Approach, 2nd Ed. 1992, pp. 1121-1127 ("Francisco"). It is noted here that Francisco is newly presented prior art. For the reasons which are set forth in detail herein, including the evidence presented in the attached Vanden Heuvel declaration, the present invention is clearly patentable.

The §103 Rejection

The Examiner has rejected claims 1-15 and 22-24 under 35 U.S.C. §103 as being obvious over de Boer, in view of Cook and Francisco. It is the Examiner's position that de Boer teaches that CLA in food compositions such as milk are useful in treating disorders such as diabetes and its symptoms such as elevated insulin and glucose intolerance. The Examiner points to column 1, lines 35-43 in support of that view. The Examiner recognizes that de Boer does not teach

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particularly that CLA is useful in a method of treating diabetes, the specific conjugated linoleic acids claimed or the amount of CLA of the present invention. The Examiner cites Cook for teaching a method of adding CLA compounds into animal feed to reduce fat in an animal and that specific isomers of octadecadienoic acid may be included in the conjugated linoleic acid. The Examiner cites Francisco for teaching that type II diabetes patients may have elevated insulin and impaired glucose tolerance.

From the teachings of the cited art the Examiner concludes that it would have been obvious to employ CLA in a method of treating diabetes and that it would have been obvious for one of ordinary skill in the art at the time the invention was made to incorporate about 1 mg to about 10,000mg/kg of body weight of the *trans,cis*-9,11-octadecadienoic acid, *cis,cis*-9,11-octadecadienoic acid or *trans,cis*-10,12-octadecadienoic acid into a milk composition product useful in a method of treating diabetes. The Examiner further argues that one of ordinary skill would have been motivated to employ CLA in a method of treating diabetes because de Boer, et al. clearly teaches that unsaturated fatty acids, including CLA, are useful in treating diabetes. It is the Examiner's conclusion, therefore, that one of ordinary skill would have reasonably *expected* that CLA would have been useful in a method of treating diabetes. Applicants respectfully traverse the Examiner's rejection.

For the reasons which are set forth in detail herein, including the evidence and papers which are presented in the attached declaration of co-inventor Vanden Heuvel, it is respectfully submitted, that contrary to the Examiner's contention, the present invention represents an unexpected result over the teachings of de Boer, Cook and Francisco. In particular, as pointed out in the attached Vanden Heuvel declaration at paragraphs 22-29, at the time of the de Boer disclosure and the filing of the present invention, it was recognized that linoleic acid, an n-6 polyunsaturated fatty acid (n-6 PUFA), having a chemical structure which is similar to CLA, exhibited no effect on diabetes type II or a *deleterious* effect on diabetes type II. Consequently, when this prior art information is viewed in relation to the disclosure of the prior art references,

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and in particular, the de Boer reference, one would invariably conclude that the instant invention is patentable.

It is respectfully submitted that the Examiner's arguments with respect to the presently pending claims are not cogent for the following reasons. First, de Boer is an ambiguous reference as to the treatment of the indicated disease states with any one or more of the indicated fatty acids and in point of fact, when read in conjunction with contemporary prior art references, cannot support the Examiner's interpretation that de Boer teaches CLA to treat diabetes. That is true based upon the fact that contemporaneous scientific studies (contemporaneous as of the filing date of the present invention and of de Boer itself) as presented in the attached Vanden Heuvel declaration evidence that not all of the fatty acids disclosed by de Boer can be used to treat the disease states cited in de Boer, and that the fatty acid closest in structure to conjugated linoleic acid, namely linoleic acid, actually was shown in the art to be either inactive or deleterious in the treatment of diabetes. Second, de Boer does not make out a cogent case that CLA itself can be used to treat the symptoms of type II diabetes mellitus of the present invention, when the type of diabetes is not mentioned by de Boer and a number of fatty acids are disclosed as having effectiveness to treat the disclosed disease states, which list includes diabetes. This is even more true given that the disclosure of de Boer does not even relate to a diabetes treatment, except in passing, and no data is posited in support of the Examiner's interpretation that de Boer stands for linoleic acid being useful in the treatment of diabetes.

As we have previously argued and as stated in the previously submitted Belury declaration at paragraph 23, diabetes is a disease state represented by at least three different disease states: Type I diabetes mellitus, Type II diabetes mellitus and diabetes insipidus. In addition, as is set forth in that declaration, it is shown that conjugated linoleic acid, alone among the fatty acids listed, is particularly effective in treating type II diabetes mellitus symptoms. Dr. Belury points out that in her own research conjugated linoleic acid has exhibited a dramatic effect on type II diabetes mellitus symptoms and linoleic acid, a fatty acid of similar chemical

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structure to CLA, showed essentially no effect on these same symptoms, whereas the Examiner's interpretation of the teachings of de Boer suggest that either of these two fatty acids can be used to treat diabetes with apparent equal effect. The attached Vanden Heuvel declaration not only corroborates the Belury declaration, but further presents evidence in *prior art documents* (see especially the Vanden Heuvel declaration at paragraph 27 and the attached references Heine, et al., *Am J Clin Nutr.* 1989 Mar;49(3):448-56; Ikemoto, et al., *Metabolism*, 1996 Dec;45(12):1539-46; and Simopoulos, *Free Radic Biol Med.* 1994 Oct;17(4):367-72, that a number of the fatty acids which are presented by de Boer (as interpreted by the Examiner) as being useful in treating diabetes, including linoleic acid are, in point of fact, either inactive or deleterious. It is Applicants' reasonable interpretation that if one of ordinary skill recognizes, as is taught in the prior art, that linoleic acid is inactive or deleterious against diabetes, that same person would expect the closely related CLA to also be inactive.

The Ambiguous, Unsupported Disclosure of De Boer, When Read in Conjunction With More Cogent Contemporaneous Scientific Studies in Reputable Journals, Does Not Support the Examiner's Interpretation of Those Teachings

As has been previously discussed, the disclosure in de Boer is ambiguous and is presented in the background portion of a patent which is directed to subject matter completely unrelated either to the present invention or to the specific use of fatty acids in treating a number of the conditions which are ambiguously referenced. There is no scientific corroboration to any of the statements made in de Boer. Specifically, it is Applicants' position is that de Boer does not propose or teach that the specific fatty acids which are generally listed are useful in treating all of the listed conditions, only that as a class, those fatty acids are useful in treating those disease states. Thus, a reasonable interpretation of the de Boer statement is that one or more of the disclosed fatty acids may be used to treat one or more of the disclosed disease states, not that each of the fatty acids disclosed therein is useful for the treatment of each of the disclosed disease states. Moreover, at the time of the present invention, it was known that oleic acid and linoleic acid were either inactive or deleterious against symptoms of type II diabetes mellitus.

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See, Ikemoto, et al., *Metabolism*, 1996 Dec;45(12):1539-46; Heine, et al., *Am J Clin Nutr*. 1989 Mar;49(3):448-56; and Simopoulos, *Free Radic Biol Med*. 1994 Oct;17(4):367-72, attached to the Vanden Heuvel declaration.^{1,2} A reasonable interpretation of de Boer, therefore, would be that one or more of the listed fatty acids might be useful to treat one or more of the disease states, but is silent as to which fatty acid is to be used to treat which disease state. Read in light of contemporaneous art which disclosed that linoleic acid is ineffective or deleterious to treat diabetes, a reasonable expectation of the skilled practitioner of the teachings of de Boer is that conjugated linoleic acid, similar in chemical structure to linoleic acid and suggested by de Boer to have similar activity, would also be inactive or deleterious.

The Examiner relies on the passage in de Boer at column 1, lines 35-42, for the teaching that CLA is useful for treating diabetes and such activity is expected. However, a review of that passage shows that the Examiner has interpreted that passage to support the view that a number of fatty acids, indeed, all of the disclosed fatty acids, including oleic acid, linoleic acid and unsaturated C₂₀ fatty acids (which description would include arachidonic acid) would also be

1 Applicants are not arguing that the de Boer passage is ambiguous because it is found in the background of the invention section of a patent rather than in the body of the specification. Rather, the passage must be viewed as ambiguous because the Examiner's interpretation directly contradicts contemporaneous teachings in the art which present experimental data in reputable scientific journals. It would seem more appropriate to consider Applicants' alternative interpretation of that passage in de Boer, given that the Examiner's interpretation is not corroborated by any teachings in de Boer and Applicants' interpretation of de Boer is corroborated by considerable contemporaneous teachings in reputable scientific journals. When an uncorroborated interpretation of a statement in a patent is contradicted by contemporaneous, experimental evidence presented in reputable scientific journal articles, considerable weight should be given to those prior art references. Otherwise, any uncorroborated statement in a patent must be considered as being irrefutable, regardless of the existence and probative value of contradictory evidence. This argument would fly in the face of a great body of patent law precedent and is untenable. We posit only that Applicants' alternative interpretation is more accurate and should be used to interpret the teachings of de Boer, rather than the Examiner's interpretation, which contradicts contemporary probative scientific evidence.

2 As an aside, the suggestion by Heine that linoleic acid may favorably influence diabetes through its putative effect on atherogenesis in diabetics is refuted by Ikemoto and Simopoulos which suggest that linoleic acid is potentially harmful in diabetes, and even Heine, itself (pages 451-452) which teaches that ischemic heart disease in diabetes is a result of hyperglycemia and hyperinsulinemia. Also, see Blankenhorn, et al., *JAMA*, 263:1646-1652 (1990) and Hodgson, et al., *Am J Clin Nutr*. 1993 Aug;58(2):228-34, both published well after Heine, et al., but before the present application, which point to the negative effects of linoleic acid in coronary heart disease. The fact that Heine acknowledges hyperinsulinemia and hyperglycemia as risk effects in coronary heart disease in diabetics (pages 451-452) and the teachings of Ikemoto and Simopoulos that linoleic acid induces or is believed to induce *unfavorable* effects on glucose tolerance and/or insulin blood levels, would preclude the use of linoleic acid for the treatment of diabetes.

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useful for the treatment of diabetes. In point of fact, the Examiner's interpretation of de Boer's statement does not square with the known activity of some of the de Boer disclosed fatty acids, inasmuch as it was known at the time of de Boer that oleic acid and linoleic acid have little, if any, use in the treatment of diabetes and in fact, may be deleterious to that disease state. Thus, the passage in de Boer is more correctly interpreted by Applicants to mean that only certain of the disclosed fatty acids could be used to influence one or more of the disease states, not that all of the fatty acids can be used to treat all of the disease states.

An alternative interpretation is that the statement in de Boer relied upon by the Examiner simply acknowledges the general understanding that existed in the art prior to the present invention that diet and in particular, the content of fatty acids within the diet, may play a role in favorably influencing of a number of disease states, including diabetes. This is further corroborated by the relevant teachings of Francisco in the second column on page 1125, which points to the total number of calories from fat and the general type of fatty acids, which could be used in a diet to favorably influence type II diabetes mellitus. However, these references fail to teach that it is only certain types of fatty acids which are particularly useful for the treatment of type II diabetes and that CLA has a unique chemical structure as an n-6 PUFA which surprisingly makes it especially effective for treating diabetes.

The unexpected activity of conjugated linoleic acid in treating type II diabetes symptoms has been presented in the previously submitted Belury declaration and is further corroborated in the attached Vanden Heuvel declaration at paragraph 26. Note that the Examiner's interpretation of the de Boer teaching would suggest that oleic acid (a monounsaturated fatty acid), linoleic acid (an n-6 polyunsaturated fatty acid or PUFA) and arachidonic acid (a C₂₀ polyunsaturated fatty acid which is also an n-6 PUFA) can be used to treat diabetes. In point of fact, these fatty acids are either inactive or *deleterious*. Thus, Applicants' respectfully submit that their interpretation of the teachings of de Boer, which suggests that only certain fatty acids disclosed therein may be useful for the treatment of one or more of the disclosed disease states,

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and that linoleic acid and CLA would act similarly in the treatment of diabetes, and be *inactive or deleterious*, is thus more accurate and consistent with the teachings of the art.

Francisco was also cited against the present invention. Francisco postulates that a diet from which no more than 30% of the caloric intake is derived from fatty acids (less than 10% from saturated fat, 10% from polyunsaturated fat and the rest from monosaturated fat) may favorably influence type II diabetes. However, as explained in the attached Vanden Heuvel declaration, a review of the literature evidences that saturated fats, monosaturated fats and n-6 polyunsaturated fats, a number of which are disclosed by de Boer, are actually inactive or deleterious to type II diabetes. Moreover, based upon the similarity of structure between the n-6 PUFAs, which were known to be inactive or deleterious in the treatment of type II diabetes, the expectation would have been for CLA, also an n-6 PUFA, not to be active. The exact opposite has been found to be true and consequently, the present invention represents an unexpected result.

Given that it was known at the time of de Boer and the invention of the present application, as evidenced by the references cited in the Vanden Heuvel declaration, that oleic acid (a monounsaturated fatty acid) and linoleic acid (an n-6 polyunsaturated acid) were either inactive or actually *deleterious* for the treatment of type II diabetes, and given the fact that CLA is also a n-6 PUFA having a chemical structure quite similar to linoleic acid³, it would have been expected at the time of the present invention, that CLA also would be inactive or actually deleterious, not *favorably active* as is taught by the present invention. This is further supported by the language in de Boer (column 1, lines 39-42) which suggests that linoleic acid and CLA act similarly ("linoleic acid which may or may not be conjugated"). Note again that de Boer does not cite any relevant data, does not provide any experimental evidence and does nothing more than provide a blanket statement of activity, which, when contrasted with conclusions drawn

³ Both linoleic acid and CLA, as well as arachidonic acid are n-6 PUFAs, which means they are polyunsaturated and have a double bond at carbon atoms 6-7 numbered from the ω position of the fatty acid. N-6 PUFAs are generally

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from published experimental data contemporary to de Boer and the present application, makes the de Boer statement at best misleading or ambiguous and arguably a teaching away from the present invention.

Thus, a fair interpretation of the de Boer passage, in light of the prior art disclosure, is that de Boer represents *at best* an invitation to experiment to determine which of the disclosed fatty acids might actually work to treat one or more of the disclosed disease states, especially diabetes, and that given that linoleic acid was taught by the art to be inactive or actually deleterious in diabetes, conjugated linoleic acid would also be expected to be inactive or deleterious. This is especially true given the prior art teachings, the chemical similarity of structure between conjugated linoleic acid and linoleic acid and the passage in de Boer suggesting their relative equivalence of activity. Thus, one of ordinary skill interpreting the teachings of de Boer would initially assume that CLA, like linoleic acid, would be inactive against diabetes. The present invention, which relies on CLA for its unique elevated activity in treating the symptoms of type II diabetes mellitus, thus represents an *unexpected result* and is clearly patentable over the teachings of de Boer.

Francisco Does Not Obviate the Deficiencies of de Boer

The Examiner has further cited Francisco in rejecting the present invention. It is noted by Applicants that Francisco does not mention CLA either literally or obliquely. Francisco is cited for generally teaching that glucose intolerance and elevated insulin levels are symptoms of type II diabetes mellitus. Other than that disclosure, Francisco is either inapposite to the present invention or simply corroborates Applicants' view that the statement of de Boer relied upon by the Examiner is ambiguous as to its teachings. Indeed, the Francisco dietary suggestions for treating type II diabetes on page 1125 are somewhat inaccurate based upon conventional knowledge and could easily be deleterious, depending upon the fatty acids employed in that diet,

inactive or deleterious against type II diabetes mellitus, with the lone exception of CLA.

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which, in Francisco, are nameless. Francisco does not specify the fatty acids to be used in the favored diet, only that a certain ratio of saturated fatty acids, monosaturated fatty acids and polyunsaturated fatty acids (without reference to the type of polyunsaturated fatty acid) should be used. However, as indicated by the Vanden Heuvel declaration, the use of saturated fatty acids, n-6 PUFAs (linoleic acid) and monounsaturated fatty acids such as oleic acid, as suggested by Francisco, were known at the time of the present application to be contraindicated. In sum, Francisco does absolutely nothing to cure the deficiencies of de Boer, and in actuality, further supports Applicants' interpretation of the de Boer statement, not the Examiner's.

The present invention is unexpected over the teachings of de Boer, in view of Francisco. Thus, de Boer cannot be cited for the proposition and there is no suggestion in de Boer that conjugated linoleic acid is a particularly effective treatment for type II diabetes mellitus symptoms, namely glucose intolerance and elevated plasma insulin and glucose, especially when other fatty acids such as the closely related linoleic acid, putatively cited for the same relative activity, are shown in contemporaneous references to have little, even deleterious activity. Francisco does not even mention CLA and as discussed above, provides inaccurate or misleading information and completely fails to obviate the deficiencies of de Boer. The present invention is therefore non-obvious over the teachings of de Boer, in view of Francisco.

Cook Does Not Obviate the Deficiencies of de Boer alone or in view of Francisco

Turning to the disclosure of Cook, this reference discloses a method of using CLA to reduce the body fat of animals, including humans. Although this reference supports the view that CLA may be used to reduce body fat and increase protein, primarily in meat animals, there is absolutely no disclosure or suggestion of the use of CLA in the treatment of type II diabetes mellitus symptoms. There is absolutely no mechanism discussed in Cook for the effects CLA exhibits in animals regarding reducing body fat. Cook provides absolutely no motivation for treating the symptoms of type II diabetes mellitus namely glucose intolerance and elevated

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plasma insulin and glucose and is respectfully believed to be inapposite to the present invention.

It is respectfully submitted that a combination of de Boer, Francisco and Cook does not disclose or suggest the present invention. There is no disclosure or suggestion that conjugated linoleic acid provides a particularly effective treatment for type II diabetes mellitus symptoms. The interpretation of the de Boer statement, as discussed above, cannot be taken to support the teaching that CLA is an especially effective treatment for diabetes and Francisco and Cook either fail to add to or clarify the teachings of de Boer.

In the present application, there is simply no cogent basis upon which to suggest that the prior art taught the use of CLA for the treatment of type II diabetes mellitus symptoms. The disclosure in de Boer does not suggest that all unsaturated fatty acids can be used to treat diabetes, because the prior art cited in the attached Vanden Heuvel declaration evidences that such an interpretation cannot be reasonably made. While the disclosure in de Boer, alone or in view of Francisco, as discussed above, does not disclose or suggest the presently claimed invention, the remaining art cited, Cook, does not disclose or suggest the treatment of diabetes *at all*. In particular, not only does Cook fail to mention diabetes, Cook fails to even mention a single symptom of diabetes set forth in the claims. As presented in the previously submitted Belury declaration at paragraph 27, there is simply no connection that can be gleaned from Cook about the role of CLA in reducing body fat and any relationship that might have to the treatment of type II diabetes mellitus. Cook is essentially inapposite to the present invention. Consequently, Applicants respectfully submit that the present invention is patentable over the disclosure of de Boer, in view of Francisco and further in view of Cook.

For the above reasons, Applicant respectfully asserts that the claims set forth in the present amendment are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

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Applicant has neither cancelled nor added any claim. No fee is therefore due for the presentation of this amendment. A petition for a one month extension of time is enclosed as is a notice of appeal. Please debit deposit account 04-0838 for the fee which is due. Large entity status now applies to the present application.

Please credit any overpayment or charge any additional fee due to Deposit Account No. 04-0838.

Respectfully submitted,

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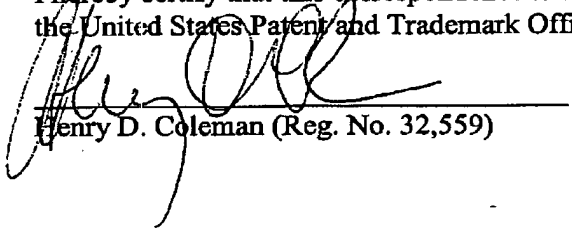
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